

**Clinical trial results:****A Multicenter, Multinational, Randomized, Double-Blind, Phase III Study of IMC-1121B Plus Docetaxel Versus Placebo Plus Docetaxel in Previously Untreated Patients with HER2-Negative, Unresectable, Locally-Recurrent or Metastatic Breast Cancer****Summary**

| | |
|--------------------------|----------------------------|
| EudraCT number | 2008-001727-65 |
| Trial protocol | ES DE BE CZ SK PL GB GR IE |
| Global end of trial date | 19 November 2020 |

Results information

| | |
|--------------------------------|---|
| Result version number | v2 (current) |
| This version publication date | 11 March 2022 |
| First version publication date | 20 November 2021 |
| Version creation reason | <ul style="list-style-type: none">• New data added to full data set New data added to full data set |

Trial information**Trial identification**

| | |
|-----------------------|-------------|
| Sponsor protocol code | I4T-IE-JVBC |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|---------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00703326 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Trial Number: 13892 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Eli Lilly and Company |
| Sponsor organisation address | Lilly Corporate Center, Indianapolis, IN, United States, 46285 |
| Public contact | Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877CTLilly, |
| Scientific contact | Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 8772854559, |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 19 November 2020 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 19 November 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to compare the progression-free survival (PFS) of the drug combination ramucirumab plus docetaxel to placebo plus docetaxel in previously untreated participants with human epidermal growth factor receptor 2 (HER2)-negative, unresectable, locally-recurrent or metastatic breast cancer.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 06 August 2008 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Australia: 49 |
| Country: Number of subjects enrolled | Brazil: 50 |
| Country: Number of subjects enrolled | Canada: 129 |
| Country: Number of subjects enrolled | Egypt: 12 |
| Country: Number of subjects enrolled | Israel: 23 |
| Country: Number of subjects enrolled | Korea, Republic of: 21 |
| Country: Number of subjects enrolled | Lebanon: 38 |
| Country: Number of subjects enrolled | New Zealand: 11 |
| Country: Number of subjects enrolled | Peru: 16 |
| Country: Number of subjects enrolled | Russian Federation: 309 |
| Country: Number of subjects enrolled | Serbia: 2 |
| Country: Number of subjects enrolled | South Africa: 63 |
| Country: Number of subjects enrolled | Taiwan: 6 |
| Country: Number of subjects enrolled | United States: 79 |
| Country: Number of subjects enrolled | Belgium: 68 |
| Country: Number of subjects enrolled | Germany: 17 |
| Country: Number of subjects enrolled | Ireland: 10 |
| Country: Number of subjects enrolled | Poland: 17 |
| Country: Number of subjects enrolled | Slovakia: 4 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Spain: 182 |
| Country: Number of subjects enrolled | Czechia: 7 |
| Country: Number of subjects enrolled | United Kingdom: 31 |
| Worldwide total number of subjects | 1144 |
| EEA total number of subjects | 305 |

Notes:

Subjects enrolled per age group

| | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 954 |
| From 65 to 84 years | 190 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Not Applicable

Pre-assignment

Screening details:

Participants who were alive and completed the follow-up period or who died were considered to have completed the study.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|-------------------------------------|
| Arm title | Ramucirumab (IMC-1121B) + Docetaxel |
|------------------|-------------------------------------|

Arm description:

Ramucirumab (IMC-1121B) is administered at a dose of 10 milligrams per kilogram (mg/kg) as a 1-hour intravenous infusion on Day 1 of each 21-day cycle. Docetaxel is administered at a dose of 75 milligrams per square meter (mg/m²) as a 1-hour intravenous infusion on Day 1 of each 21-day cycle.

| | |
|--|-------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ramucirumab (IMC-1121B) |
| Investigational medicinal product code | |
| Other name | IMC-1121B,LY3009806 |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Ramucirumab (IMC-1121B) is administered at a dose of 10 mg/kg as a 1-hour intravenous infusion on Day 1 of each 21-day cycle.

| | |
|--|-----------------------|
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Docetaxel is administered at a dose of 75 milligrams per square meter (mg/m²) as a 1-hour intravenous infusion on Day 1 of each 21-day cycle.

| | |
|------------------|---------------------|
| Arm title | Placebo + Docetaxel |
|------------------|---------------------|

Arm description:

Placebo comparator for ramucirumab (IMC-1121B) administered at a dose of 10 mg/kg as a 1-hour intravenous infusion on Day 1 of each 21-day cycle. Docetaxel is administered at a dose of 75 milligrams per square meter (mg/m²) as a 1-hour intravenous infusion on Day 1 of each 21-day cycle.

| | |
|--|-----------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Docetaxel is administered at a dose of 75 milligrams per square meter (mg/m²) as a 1-hour intravenous infusion on Day 1 of each 21-day cycle.

| | |
|--|-----------------------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | placebo |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Placebo comparator for ramucirumab (IMC-1121B) administered at a dose of 10 mg/kg as a 1-hour intravenous infusion on Day 1 of each 21-day cycle.

| Number of subjects in period 1 | Ramucirumab (IMC-1121B) + Docetaxel | Placebo + Docetaxel |
|--|-------------------------------------|---------------------|
| Started | 759 | 385 |
| Received at least 1 dose of study drug | 752 | 382 |
| Completed | 657 | 347 |
| Not completed | 102 | 38 |
| Consent withdrawn by subject | 54 | 20 |
| Adverse event, non-fatal | 1 | - |
| Lost to follow-up | 47 | 18 |

Baseline characteristics

Reporting groups

| | |
|--|-------------------------------------|
| Reporting group title | Ramucirumab (IMC-1121B) + Docetaxel |
| Reporting group description: | |
| Ramucirumab (IMC-1121B) is administered at a dose of 10 milligrams per kilogram (mg/kg) as a 1-hour intravenous infusion on Day 1 of each 21-day cycle. Docetaxel is administered at a dose of 75 milligrams per square meter (mg/m ²) as a 1-hour intravenous infusion on Day 1 of each 21-day cycle. | |
| Reporting group title | Placebo + Docetaxel |
| Reporting group description: | |
| Placebo comparator for ramucirumab (IMC-1121B) administered at a dose of 10 mg/kg as a 1-hour intravenous infusion on Day 1 of each 21-day cycle. Docetaxel is administered at a dose of 75 milligrams per square meter (mg/m ²) as a 1-hour intravenous infusion on Day 1 of each 21-day cycle. | |

| Reporting group values | Ramucirumab (IMC-1121B) + Docetaxel | Placebo + Docetaxel | Total |
|------------------------|-------------------------------------|---------------------|-------|
| Number of subjects | 759 | 385 | 1144 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|--|--------|--------|------|
| Age continuous | | | |
| Intent-to-Treat (ITT) Population: All randomized participants. | | | |
| Units: years | | | |
| arithmetic mean | 53.9 | 54.2 | |
| standard deviation | ± 10.5 | ± 10.0 | - |
| Gender categorical | | | |
| Intent-to-Treat (ITT) Population: All randomized participants. | | | |
| Units: Subjects | | | |
| Female | 759 | 385 | 1144 |
| Male | 0 | 0 | 0 |
| Ethnicity (NIH/OMB) | | | |
| Intent-to-Treat (ITT) Population: All randomized participants. | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 69 | 42 | 111 |
| Not Hispanic or Latino | 690 | 343 | 1033 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Region of Enrollment | | | |
| Units: Subjects | | | |
| Serbia | 0 | 2 | 2 |
| United States | 58 | 21 | 79 |
| Taiwan | 4 | 2 | 6 |
| Slovakia | 2 | 2 | 4 |
| Spain | 118 | 64 | 182 |
| Lebanon | 24 | 14 | 38 |
| Ireland | 8 | 2 | 10 |
| Russian Federation | 210 | 99 | 309 |
| Israel | 16 | 7 | 23 |
| United Kingdom | 21 | 10 | 31 |
| Egypt | 9 | 3 | 12 |
| Czech Republic | 4 | 3 | 7 |

| | | | |
|--|-----|-----|------|
| Canada | 83 | 46 | 129 |
| Poland | 12 | 5 | 17 |
| Belgium | 48 | 20 | 68 |
| Brazil | 30 | 20 | 50 |
| Peru | 12 | 4 | 16 |
| Australia | 28 | 21 | 49 |
| South Africa | 41 | 22 | 63 |
| Germany | 12 | 5 | 17 |
| New Zealand | 5 | 6 | 11 |
| South Korea | 14 | 7 | 21 |
| Race | | | |
| Intent-to-Treat (ITT) Population: All randomized participants. | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 1 | 1 | 2 |
| Asian | 31 | 20 | 51 |
| Native Hawaiian or Other Pacific Islander | 2 | 0 | 2 |
| Black or African American | 27 | 14 | 41 |
| White | 676 | 341 | 1017 |
| Other | 22 | 9 | 31 |

End points

End points reporting groups

| | |
|--|-------------------------------------|
| Reporting group title | Ramucirumab (IMC-1121B) + Docetaxel |
| Reporting group description: Ramucirumab (IMC-1121B) is administered at a dose of 10 milligrams per kilogram (mg/kg) as a 1-hour intravenous infusion on Day 1 of each 21-day cycle. Docetaxel is administered at a dose of 75 milligrams per square meter (mg/m ²) as a 1-hour intravenous infusion on Day 1 of each 21-day cycle. | |
| Reporting group title | Placebo + Docetaxel |
| Reporting group description: Placebo comparator for ramucirumab (IMC-1121B) administered at a dose of 10 mg/kg as a 1-hour intravenous infusion on Day 1 of each 21-day cycle. Docetaxel is administered at a dose of 75 milligrams per square meter (mg/m ²) as a 1-hour intravenous infusion on Day 1 of each 21-day cycle. | |

Primary: Progression-Free Survival (PFS)

| | |
|---|---------------------------------|
| End point title | Progression-Free Survival (PFS) |
| End point description: PFS defined as time from randomization until the first evidence of progression as defined by Response Evaluation Criteria in Solid Tumors (RECIST v1.0) or death from any cause; by Investigator assessment. Progressive disease (PD) defined as at least a 20% increase in sum of longest diameter of target lesions taking as reference the smallest sum longest diameter since baseline, progression in non-target lesions or the appearance of 1 or more new lesion(s). Participants who neither progressed nor died were censored the day of their last radiographic tumor assessment if available or date of randomization if no post initiation radiographic assessment was available. If death or PD occurred after ≥2 missing radiographic visits, censoring occurred at date of last radiographic visit prior to the missed visits. The symptomatic/clinical disease progression (deterioration) without documented radiologic progression did not constitute progression. Censored participants: ramucirumab + docetaxel=94. | |
| End point type | Primary |
| End point timeframe: Randomization to disease progression or death or until data cutoff of 31 Mar 2013 (up to 56 months) | |

| End point values | Ramucirumab (IMC-1121B) + Docetaxel | Placebo + Docetaxel | | |
|----------------------------------|-------------------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 759 ^[1] | 385 ^[2] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 9.5 (8.3 to 9.8) | 8.2 (7.1 to 8.5) | | |

Notes:

[1] - Intent-to-Treat (ITT) Population: All randomized participants.

[2] - Intent-to-Treat (ITT) Population: All randomized participants.

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Progression-Free Survival (PFS) |
| Statistical analysis description: Hazard ratio (HR) with 95% confidence interval (CI) was estimated using a stratified Cox proportional hazards regression model using the Interactive Web Response System (IWRS) stratification factors. | |
| Comparison groups | Ramucirumab (IMC-1121B) + Docetaxel v Placebo + Docetaxel |

| | |
|---|---------------------------|
| Number of subjects included in analysis | 1144 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[3] |
| P-value | = 0.077 ^[4] |
| Method | Stratified Log Rank (SLR) |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.88 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.75 |
| upper limit | 1.01 |

Notes:

[3] - Analysis type: Superiority or Other (legacy)

[4] - SLR used Interactive Web Response System (IWRS) factors: prior taxane therapy, visceral metastasis, hormone receptor status and geographical regions.

Secondary: Overall Survival (OS)

| | |
|--|-----------------------|
| End point title | Overall Survival (OS) |
| End point description: | |
| OS was defined as the duration from randomization to death from any cause. Participants who were alive at data cut-off for the OS analysis or lost to follow-up were censored on the last date the participant was known to be alive. Censored participants: ramucirumab + docetaxel=267, placebo + docetaxel=121. | |
| End point type | Secondary |
| End point timeframe: | |
| Randomization to death or until data cutoff of 29-May-2015 (up to 82 months) | |

| End point values | Ramucirumab (IMC-1121B) + Docetaxel | Placebo + Docetaxel | | |
|----------------------------------|-------------------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 759 ^[5] | 385 ^[6] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 30.3 (27.5 to 33.5) | 28.7 (25.6 to 32.3) | | |

Notes:

[5] - Intent-to-Treat (ITT) Population: All randomized participants.

[6] - Intent-to-Treat (ITT) Population: All randomized participants.

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Overall Survival (OS) |
| Statistical analysis description: | |
| SLR used Interactive Web Response System (IWRS) factors: prior taxane therapy, visceral metastasis, hormone receptor status and geographical regions. HR with 95% confidence interval (CI) was estimated using a stratified Cox proportional hazards regression model using the IWRS stratification factors. | |
| Comparison groups | Ramucirumab (IMC-1121B) + Docetaxel v Placebo + Docetaxel |

| | |
|---|---------------------------|
| Number of subjects included in analysis | 1144 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[7] |
| P-value | = 0.487 ^[8] |
| Method | Stratified Log Rank (SLR) |
| Parameter estimate | Hazard ratio (HR) |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.81 |
| upper limit | 1.1 |

Notes:

[7] - Superiority or Other (legacy)

[8] - The gate-keeping strategy used to control overall type 1 error 0.05 (2-sided) or 0.025 (1-sided) to analyze progression-free survival (PFS) and OS. At final PFS analysis only if primary PFS test was significant would analysis of OS be inferential.

Secondary: Time to Progression (TTP)

| | |
|-----------------|---------------------------|
| End point title | Time to Progression (TTP) |
|-----------------|---------------------------|

End point description:

TTP was defined as time from the date of randomization to first documented date of disease progression using Response Evaluation Criteria in Solid Tumors (RECIST v1.0) criteria; by Investigator assessment. Progressive disease (PD) was defined as at least a 20% increase in sum of longest diameter (LD) of target lesions taking as reference smallest sum LD since baseline, progression in non-target lesions or the appearance of 1 or more new lesion(s). Participants who did not progress were censored at the last radiographic tumor assessment. If no post-baseline assessment was available censoring occurred at the date of randomization. If PD occurred after 2 or more missing radiographic visits, censoring occurred at the date of the last radiographic visit prior to the missed visits. The symptomatic/clinical disease progression (deterioration) without documented radiologic progression did not constitute progression. Censored participants: ramucirumab + docetaxel=263, placebo + docetaxel=104.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Randomization to disease progression or until data cutoff of 31-Mar-2013 (up to 56 months)

| End point values | Ramucirumab (IMC-1121B) + Docetaxel | Placebo + Docetaxel | | |
|----------------------------------|-------------------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 759 ^[9] | 385 ^[10] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 11.4 (10.7 to 13.3) | 9.7 (8.2 to 10.9) | | |

Notes:

[9] - Intent-to-Treat (ITT) Population: All randomized participants.

[10] - Intent-to-Treat (ITT) Population: All randomized participants.

Statistical analyses

| | |
|----------------------------|---------------------------|
| Statistical analysis title | Time to Progression (TTP) |
|----------------------------|---------------------------|

Statistical analysis description:

HR with 95% CI was estimated using a stratified Cox proportional hazards regression model using the IWRS stratification factors.

| | |
|-------------------|---|
| Comparison groups | Ramucirumab (IMC-1121B) + Docetaxel v Placebo + Docetaxel |
|-------------------|---|

| | |
|---|---------------------------|
| Number of subjects included in analysis | 1144 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[11] |
| P-value | = 0.033 ^[12] |
| Method | Stratified Log Rank (SLR) |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.73 |
| upper limit | 0.99 |

Notes:

[11] - Superiority or Other (legacy)

[12] - SLR used Interactive Web Response System (IWRS) factors: prior taxane therapy, visceral metastasis, hormone receptor status and geographical regions.

Secondary: Percentage of Participants with Complete Response (CR) or Partial Response (PR) (Objective Response Rate)

| | |
|-----------------|---|
| End point title | Percentage of Participants with Complete Response (CR) or Partial Response (PR) (Objective Response Rate) |
|-----------------|---|

End point description:

Objective response rate (ORR) was defined as the percentage of randomized participants achieving a best confirmed overall response of CR or PR using Response Evaluation Criteria in Solid Tumors (RECIST v1.0), based on the achievement of both measurement and confirmation criteria; by Investigator assessment. CR was defined as the disappearance of all target and non-target lesions. PR was defined as at least a 30% decrease in the sum of the longest diameters (LD) of target lesions, taking as reference the baseline sum LD and no progression in non-target lesions.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Randomization to disease progression or until data cutoff of 31-Mar-2013 (up to 56 months)

| End point values | Ramucirumab (IMC-1121B) + Docetaxel | Placebo + Docetaxel | | |
|-----------------------------------|-------------------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 759 ^[13] | 385 ^[14] | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 44.7 (41.1 to 48.3) | 37.9 (33.1 to 43.0) | | |

Notes:

[13] - Intent-to-Treat (ITT) Population: All randomized participants.

[14] - Intent-to-Treat (ITT) Population: All randomized participants.

Statistical analyses

| | |
|----------------------------|-------------------------|
| Statistical analysis title | Objective Response Rate |
|----------------------------|-------------------------|

Statistical analysis description:

Stratified odds ratio was calculated considering the IWRS stratification factors.

| | |
|-------------------|---|
| Comparison groups | Placebo + Docetaxel v Ramucirumab (IMC-1121B) + Docetaxel |
|-------------------|---|

| | |
|---|--|
| Number of subjects included in analysis | 1144 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[15] |
| P-value | = 0.027 ^[16] |
| Method | Stratified Cochran-Mantel-Haenszel(SCMH) |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.33 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.03 |
| upper limit | 1.71 |

Notes:

[15] - Superiority or Other (legacy)

[16] - SCMH used Interactive Web Response System (IWRS) factors: prior taxane therapy, visceral metastasis, hormone receptor status and geographical regions.

Secondary: Duration of Response

| | |
|--|----------------------|
| End point title | Duration of Response |
| End point description: | |
| Duration of complete response (CR) or partial response (PR) measured from time criteria were first met for CR or PR until first date of progressive disease (PD) or death from any cause defined using RECIST 1.0; by Investigator assessment.CR defined as disappearance of all target and non-target lesions.PR defined as ≥30% decrease in sum of LD of target lesions and no progression in non-target lesions.PD defined as ≥20% increase in LD sum of target lesions taking as reference the smallest sum LD since baseline,progression in non-target lesions or the appearance of ≥1 new lesion(s).Participants who did not relapse or die censored at day of last radiographic tumor assessment.If death or PD was after ≥2 missing radiographic visits, censoring was at date of last radiographic visit prior to missed visits.Symptomatic/clinical disease progression without documented radiologic progression did not constitute progression. Censored participants: ramucirumab + docetaxel=80, placebo + docetaxel=28. | |
| End point type | Secondary |
| End point timeframe: | |
| Date of first CR or PR to PD or death or until data cutoff date of 31-Mar-2013 (up to 56 months) | |

| End point values | Ramucirumab (IMC-1121B) + Docetaxel | Placebo + Docetaxel | | |
|----------------------------------|-------------------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 339 ^[17] | 146 ^[18] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 8.4 (8.0 to 9.7) | 8.1 (6.8 to 8.9) | | |

Notes:

[17] - A subset of the Intent-to-Treat (ITT) Population: all randomized participants with CR or PR.

[18] - A subset of the Intent-to-Treat (ITT) Population: all randomized participants with CR or PR.

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Duration of Response |
| Statistical analysis description: | |
| HR with 95% CI was estimated using a stratified Cox proportional hazards regression model using the IWRS stratification factors. | |
| Comparison groups | Ramucirumab (IMC-1121B) + Docetaxel v Placebo + Docetaxel |

| | |
|---|---------------------------|
| Number of subjects included in analysis | 485 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[19] |
| P-value | = 0.15 ^[20] |
| Method | Stratified Log Rank (SLR) |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.84 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.67 |
| upper limit | 1.06 |

Notes:

[19] - Superiority or Other (legacy)

[20] - SLR used Interactive Web Response System (IWRS) factors: prior taxane therapy, visceral metastasis, hormone receptor status and geographical regions.

Secondary: Total Functional Assessment of Cancer Therapy-Breast (FACT-B): Change From Baseline to End of Therapy

| | |
|-----------------|---|
| End point title | Total Functional Assessment of Cancer Therapy-Breast (FACT-B): Change From Baseline to End of Therapy |
|-----------------|---|

End point description:

FACT-B measures the following domains of health-related quality of life (HR-QoL): physical well-being (PWB), social/family well-being (SFWB), emotional well-being (EWB), functional well-being (FWB), and additional concerns of breast cancer subscale (BCS) each with 6 or more items developed to measure problems specific to breast cancer symptoms plus additional items related to global QoL. Participants (pts) respond to each of the 36 questions on a 5-point scale from 0 (not at all) to 4 (very much) with a total scores range of 0-144. Higher scores indicate fewer symptoms and better HR-QoL.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, End of Therapy or until data cutoff of 31-Mar-2013 (up to 56 months)

| End point values | Ramucirumab (IMC-1121B) + Docetaxel | Placebo + Docetaxel | | |
|--------------------------------------|-------------------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 494 ^[21] | 251 ^[22] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | -6.8 (± 17.3) | -7.0 (± 16.8) | | |

Notes:

[21] - A subset of ITT Population: all randomized pts with a valid baseline and end of therapy assessments.

[22] - A subset of ITT Population: all randomized pts with a valid baseline and end of therapy assessments.

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | FACT-B: Change From Baseline to End of Therapy |
| Comparison groups | Ramucirumab (IMC-1121B) + Docetaxel v Placebo + Docetaxel |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 745 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[23] |
| P-value | = 0.539 ^[24] |
| Method | ANCOVA |

Notes:

[23] - Superiority or Other (legacy)

[24] - P-value is for end of therapy. Analysis of covariance (ANCOVA) adjusted for baseline score was used to compare the 2 treatment arms.

Secondary: Number of Participants with Adverse Events

| | |
|-----------------|--|
| End point title | Number of Participants with Adverse Events |
|-----------------|--|

End point description:

Clinically significant events were defined as serious adverse events (SAE) and other treatment-emergent non-serious adverse events (NSAE). A summary of SAEs and other NSAEs is located in the Reported Adverse Event module.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

First dose to study completion (up to 12.3 years)

| End point values | Ramucirumab (IMC-1121B) + Docetaxel | Placebo + Docetaxel | | |
|-----------------------------|-------------------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 752 ^[25] | 382 ^[26] | | |
| Units: participants | | | | |
| number (not applicable) | | | | |
| Participants with SAEs | 286 | 117 | | |
| Participants with NSAEs | 738 | 373 | | |

Notes:

[25] - All randomized participants who received at least 1 dose of study drug.

[26] - All randomized participants who received at least 1 dose of study drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity: Percentage of Participants With Treatment Emergent Anti-Ramucirumab Antibodies Until Primary Data Cutoff of 31-Mar-2013

| | |
|-----------------|---|
| End point title | Immunogenicity: Percentage of Participants With Treatment Emergent Anti-Ramucirumab Antibodies Until Primary Data Cutoff of 31-Mar-2013 |
|-----------------|---|

End point description:

Percentage of participants with treatment-emergent positive for anti-ramucirumab (IMC-1121B) antibodies during the study. Participants were considered positive for anti-ramucirumab (IMC-1121B) antibodies if they exhibited a post-treatment antibody level that exceeded the positive upper cut point determined from the anti-ramucirumab (IMC-1121B) level seen in healthy untreated individuals. Analysis population included all randomized participants who received at least 1 dose of study drug with anti-IMC-1121B antibodies samples collected during the study.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, prior to cycle 3 infusion, prior to cycle 5 infusion, onset of infusion reaction, resolution of reaction and 30 days following the event up to 56 months

| End point values | Ramucirumab (IMC-1121B) + Docetaxel | Placebo + Docetaxel | | |
|-----------------------------------|-------------------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 715 | 360 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 0.8 | 0.8 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity: Percentage of Participants Available After 31-Mar-2013 With Treatment Emergent Anti-Ramucirumab Antibodies Until Data Cutoff From 01-Apr-2013 to 08-Sep-2016

| | |
|-----------------|--|
| End point title | Immunogenicity: Percentage of Participants Available After 31-Mar-2013 With Treatment Emergent Anti-Ramucirumab Antibodies Until Data Cutoff From 01-Apr-2013 to 08-Sep-2016 |
|-----------------|--|

End point description:

Percentage of participants with treatment-emergent positive for anti-ramucirumab (IMC-1121B) antibodies during the study. Participants were considered positive for anti-ramucirumab (IMC-1121B) antibodies if they exhibited a post-treatment antibody level that exceeded the positive upper cut point determined from the anti-ramucirumab (IMC-1121B) level seen in healthy untreated individuals. Analysis population included all follow-up participants (additional participants who were available after primary data cut off 31-Mar-13) who received at least 1 dose of study drug with anti-IMC-1121B antibodies samples collected during the study.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Follow-up from 01-Apr-2013 to 08-Sep-2016 (Up to 56 -97 months)

| End point values | Ramucirumab (IMC-1121B) + Docetaxel | Placebo + Docetaxel | | |
|-----------------------------------|-------------------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 35 | 22 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose to study completion (up to 12.3 years)

Adverse event reporting additional description:

All randomized participants who received at least 1 dose of study drug. Disease progression without clinical manifestation or death related to progressive disease (PD) was not to be reported as an AE. However, all deaths within 30 days of last dose reported as SAE, regardless of causality. PD itself reported as an SAE, if any of the SAE criteria met.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | Placebo + Docetaxel |
|-----------------------|---------------------|

Reporting group description:

Placebo comparator for ramucirumab (IMC-1121B) administered at a dose of 10 mg/kg as a 1-hour intravenous infusion on Day 1 of each 21-day cycle. Docetaxel is administered at a dose of 75 milligrams per square meter (mg/m²) as a 1-hour intravenous infusion on Day 1 of each 21-day cycle.

| | |
|-----------------------|-------------------------------------|
| Reporting group title | Ramucirumab (IMC-1121B) + Docetaxel |
|-----------------------|-------------------------------------|

Reporting group description:

Ramucirumab (IMC-1121B) is administered at a dose of 10 milligrams per kilogram (mg/kg) as a 1-hour intravenous infusion on Day 1 of each 21-day cycle. Docetaxel is administered at a dose of 75 milligrams per square meter (mg/m²) as a 1-hour intravenous infusion on Day 1 of each 21-day cycle.

| Serious adverse events | Placebo + Docetaxel | Ramucirumab (IMC-1121B) + Docetaxel | |
|---|---------------------|-------------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 117 / 382 (30.63%) | 285 / 752 (37.90%) | |
| number of deaths (all causes) | 9 | 30 | |
| number of deaths resulting from adverse events | 1 | 9 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| acute myeloid leukaemia | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| breast cancer | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |

| | | | | |
|--|-----------------|-----------------|--|--|
| colon cancer | | | | |
| alternative dictionary used: MedDRA 18.0 | | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| haemangioma | | | | |
| alternative dictionary used: MedDRA 18.0 | | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| malignant ascites | | | | |
| alternative dictionary used: MedDRA 18.0 | | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| malignant neoplasm progression | | | | |
| alternative dictionary used: MedDRA 18.0 | | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| malignant pleural effusion | | | | |
| alternative dictionary used: MedDRA 18.0 | | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| metastases to central nervous system | | | | |
| alternative dictionary used: MedDRA 18.0 | | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 3 / 752 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | | |
| metastases to meninges | | | | |
| alternative dictionary used: MedDRA 18.0 | | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| neoplasm progression | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 4 / 752 (0.53%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 4 | |
| tumour embolism | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Vascular disorders | | | |
| deep vein thrombosis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 3 / 382 (0.79%) | 2 / 752 (0.27%) | |
| occurrences causally related to treatment / all | 3 / 3 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| embolism | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hypertension | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hypertensive crisis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hypotension | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 2 / 382 (0.52%) | 4 / 752 (0.53%) | |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| jugular vein thrombosis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| lymphoedema | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| subclavian vein thrombosis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| thrombosis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| therapy change | | | |
| alternative dictionary used: MedDRA 18.0 | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| asthenia | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 5 / 752 (0.66%) | |
| occurrences causally related to treatment / all | 1 / 1 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| chills | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 3 / 752 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| complication associated with device | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 2 / 382 (0.52%) | 2 / 752 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| death | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 2 / 752 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 2 / 2 | |
| disease progression | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 4 / 382 (1.05%) | 8 / 752 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 8 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 6 | |
| extravasation | | | |
| alternative dictionary used: MedDRA 18.0 | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| face oedema | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 2 / 752 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| fatigue | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 10 / 752 (1.33%) | |
| occurrences causally related to treatment / all | 1 / 1 | 9 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| general physical health deterioration | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 2 / 752 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| generalised oedema | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 2 / 752 (0.27%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| inflammation | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| infusion site thrombosis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|-----------------|-----------------|--|
| malaise | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| mucosal inflammation | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| multiple organ dysfunction syndrome | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| oedema | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| oedema peripheral | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 2 / 752 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pyrexia | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 2 / 382 (0.52%) | 8 / 752 (1.06%) | |
| occurrences causally related to treatment / all | 1 / 2 | 6 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| sudden death | | | |
| alternative dictionary used: MedDRA 18.0 | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 382 (0.00%) | 2 / 752 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Immune system disorders | | | |
| hypersensitivity | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 3 / 382 (0.79%) | 4 / 752 (0.53%) | |
| occurrences causally related to treatment / all | 3 / 3 | 4 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Social circumstances | | | |
| disability | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| menstruation irregular | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| uterine haemorrhage | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| uterine polyp | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| vaginal haemorrhage | | | |
| alternative dictionary used: MedDRA 18.0 | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| acute interstitial pneumonitis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| dyspnoea | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 5 / 382 (1.31%) | 5 / 752 (0.66%) | |
| occurrences causally related to treatment / all | 2 / 6 | 3 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| epistaxis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 2 / 752 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| haemoptysis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| interstitial lung disease | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| lung infiltration | | | |
| alternative dictionary used: MedDRA 18.0 | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pleural effusion | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 6 / 382 (1.57%) | 8 / 752 (1.06%) | |
| occurrences causally related to treatment / all | 2 / 7 | 5 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pneumonitis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pneumothorax | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 3 / 752 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pulmonary embolism | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 4 / 382 (1.05%) | 3 / 752 (0.40%) | |
| occurrences causally related to treatment / all | 3 / 4 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| respiratory failure | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| anxiety | | | |
| alternative dictionary used: MedDRA 18.0 | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| confusional state | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 4 / 752 (0.53%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| depression | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| mood altered | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 2 / 382 (0.52%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |
| thrombosis in device | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| blood calcium decreased | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| neutrophil count decreased | | | |
| alternative dictionary used: MedDRA 18.0 | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| ankle fracture | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| chemical burn of skin | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| expired product administered | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| facial bones fracture | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| femur fracture | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hip fracture | | | |
| alternative dictionary used: MedDRA 18.0 | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 382 (0.26%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| humerus fracture | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ilium fracture | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| incorrect dose administered | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| infusion related reaction | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 3 / 752 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| injury | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| medication error | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 2 / 382 (0.52%) | 9 / 752 (1.20%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | | |
|--|-----------------|-----------------|--|--|
| overdose | | | | |
| alternative dictionary used: MedDRA 18.0 | | | | |
| subjects affected / exposed | 5 / 382 (1.31%) | 7 / 752 (0.93%) | | |
| occurrences causally related to treatment / all | 1 / 11 | 4 / 13 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| procedural pneumothorax | | | | |
| alternative dictionary used: MedDRA 18.0 | | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| product administration error | | | | |
| alternative dictionary used: MedDRA 18.0 | | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| product dispensing error | | | | |
| alternative dictionary used: MedDRA 18.0 | | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 3 / 752 (0.40%) | | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| product preparation issue | | | | |
| alternative dictionary used: MedDRA 18.0 | | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| radiation oesophagitis | | | | |
| alternative dictionary used: MedDRA 18.0 | | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| spinal fracture | | | | |
| alternative dictionary used: MedDRA 18.0 | | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| stoma site haemorrhage | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| suture rupture | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| underdose | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 12 / 382 (3.14%) | 11 / 752 (1.46%) | |
| occurrences causally related to treatment / all | 0 / 24 | 4 / 34 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| wound dehiscence | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| wrong product administered | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| atrial fibrillation | | | |
| alternative dictionary used: MedDRA 18.0 | | | |

| | | | | |
|---|-----------------|-----------------|--|--|
| subjects affected / exposed | 1 / 382 (0.26%) | 1 / 752 (0.13%) | | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| atrial flutter | | | | |
| alternative dictionary used: MedDRA 18.0 | | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| cardiac failure congestive | | | | |
| alternative dictionary used: MedDRA 18.0 | | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| left ventricular dysfunction | | | | |
| alternative dictionary used: MedDRA 18.0 | | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| myocardial infarction | | | | |
| alternative dictionary used: MedDRA 18.0 | | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 2 / 752 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| pericarditis | | | | |
| alternative dictionary used: MedDRA 18.0 | | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| pericarditis constrictive | | | | |
| alternative dictionary used: MedDRA 18.0 | | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |

| | | | |
|---|-----------------|-----------------|--|
| right ventricular failure alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| supraventricular tachycardia alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| tachycardia alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 2 / 382 (0.52%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| cerebral haemorrhage alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| cerebral ischaemia alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| cerebrovascular accident alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| demyelinating polyneuropathy alternative dictionary used: MedDRA 18.0 | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| dizziness | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| encephalopathy | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 2 / 752 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| epilepsy | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| haemorrhagic stroke | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| headache | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 7 / 752 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hepatic encephalopathy | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

| | | | |
|--|-----------------|-----------------|--|
| hydrocephalus | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| loss of consciousness | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| migraine | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| nervous system disorder | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| neuropathy peripheral | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| paraplegia | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| peripheral motor neuropathy | | | |
| alternative dictionary used: MedDRA 18.0 | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| peripheral sensory neuropathy alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 2 / 752 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| radiculopathy alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| seizure alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 2 / 752 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| subarachnoid haemorrhage alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| syncope alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| transient ischaemic attack alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|------------------|------------------|--|
| Blood and lymphatic system disorders | | | |
| anaemia | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 3 / 382 (0.79%) | 2 / 752 (0.27%) | |
| occurrences causally related to treatment / all | 3 / 4 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| disseminated intravascular coagulation | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 2 / 752 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| febrile neutropenia | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 11 / 382 (2.88%) | 51 / 752 (6.78%) | |
| occurrences causally related to treatment / all | 12 / 12 | 57 / 57 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| neutropenia | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 20 / 382 (5.24%) | 47 / 752 (6.25%) | |
| occurrences causally related to treatment / all | 23 / 23 | 52 / 52 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| thrombocytopenia | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 2 / 752 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| vertigo | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |

| | | | |
|--|-----------------|-----------------|--|
| dacryostenosis acquired alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| panophthalmitis alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| papilloedema alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| visual acuity reduced alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| abdominal pain alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 4 / 752 (0.53%) | |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| anal fistula alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ascites alternative dictionary used: MedDRA 18.0 | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| colitis ischaemic | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| constipation | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 3 / 752 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| diarrhoea | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 2 / 382 (0.52%) | 9 / 752 (1.20%) | |
| occurrences causally related to treatment / all | 2 / 2 | 9 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| diverticular perforation | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 4 / 752 (0.53%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| duodenitis haemorrhagic | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| enterocolitis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |

| | | | |
|--|-----------------|-----------------|--|
| faecaloma | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| gastric ulcer perforation | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| gastritis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| haemorrhoids | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 2 / 752 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ileus | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ileus paralytic | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| intestinal pseudo-obstruction | | | |
| alternative dictionary used: MedDRA 18.0 | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| large intestinal ulcer | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| large intestine perforation | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 3 / 752 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| mouth haemorrhage | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| nausea | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 5 / 752 (0.66%) | |
| occurrences causally related to treatment / all | 1 / 1 | 5 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| oesophagitis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 2 / 752 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pancreatitis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|-----------------|-----------------|--|
| rectal haemorrhage | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| retroperitoneal fibrosis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| small intestinal haemorrhage | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| stomatitis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 9 / 752 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 11 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| vomiting | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 2 / 382 (0.52%) | 7 / 752 (0.93%) | |
| occurrences causally related to treatment / all | 2 / 2 | 6 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| cholecystitis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| cholelithiasis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hepatic failure | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 2 / 752 (0.27%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 1 | |
| hepatic function abnormal | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 2 / 752 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| hepatic pain | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hyperbilirubinaemia | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| liver disorder | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 2 / 752 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| dermatitis allergic | | | |
| alternative dictionary used: MedDRA 18.0 | | | |

| | | | | |
|---|-----------------|-----------------|--|--|
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| erythema nodosum | | | | |
| alternative dictionary used: MedDRA 18.0 | | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| lichen sclerosus | | | | |
| alternative dictionary used: MedDRA 18.0 | | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| palmar-plantar erythrodysaesthesia syndrome | | | | |
| alternative dictionary used: MedDRA 18.0 | | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| rash | | | | |
| alternative dictionary used: MedDRA 18.0 | | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| skin ulcer | | | | |
| alternative dictionary used: MedDRA 18.0 | | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| subcutaneous emphysema | | | | |
| alternative dictionary used: MedDRA 18.0 | | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| acute kidney injury | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 5 / 752 (0.66%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 2 / 2 | |
| dysuria | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| proteinuria | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 2 / 752 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| renal failure | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| renal impairment | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ureteric obstruction | | | |
| alternative dictionary used: MedDRA 18.0 | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| urinary retention | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| arthralgia | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 3 / 752 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| back pain | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 3 / 752 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| bone pain | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 3 / 752 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| muscular weakness | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| musculoskeletal chest pain | | | |
| alternative dictionary used: MedDRA 18.0 | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 382 (0.00%) | 2 / 752 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| musculoskeletal pain | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 2 / 752 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| myalgia | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| myositis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| osteonecrosis of jaw | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 2 / 752 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pain in extremity | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 2 / 752 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pathological fracture | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 2 / 752 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|--|
| spinal pain alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 382 (0.00%) 0 / 0 0 / 0 | 1 / 752 (0.13%) 0 / 1 0 / 0 | |
| Infections and infestations | | | |
| abdominal infection alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 382 (0.00%) 0 / 0 0 / 0 | 1 / 752 (0.13%) 1 / 1 0 / 0 | |
| abdominal wall abscess alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 382 (0.00%) 0 / 0 0 / 0 | 1 / 752 (0.13%) 1 / 1 0 / 0 | |
| abscess intestinal alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 382 (0.00%) 0 / 0 0 / 0 | 1 / 752 (0.13%) 1 / 1 0 / 0 | |
| abscess limb alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 382 (0.26%) 0 / 1 0 / 0 | 1 / 752 (0.13%) 0 / 1 0 / 0 | |
| abscess soft tissue alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 382 (0.00%) 0 / 0 0 / 0 | 1 / 752 (0.13%) 0 / 1 0 / 0 | |
| anal abscess alternative dictionary used: MedDRA 18.0 | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 382 (0.26%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| anal infection | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| bronchitis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 3 / 752 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| catheter site infection | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| cellulitis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 8 / 752 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 7 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| clostridium difficile colitis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| clostridium difficile infection | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|-----------------|-----------------|--|
| device related infection | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 2 / 752 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| diverticulitis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| gastroenteritis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| gastroenteritis viral | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| infection | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 4 / 752 (0.53%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| lower respiratory tract infection | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 3 / 752 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| lymphangitis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| mastitis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| mucosal infection | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| neutropenic infection | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 9 / 382 (2.36%) | 19 / 752 (2.53%) | |
| occurrences causally related to treatment / all | 10 / 10 | 18 / 19 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| neutropenic sepsis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 7 / 752 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 6 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| oral herpes | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| osteomyelitis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|-----------------|------------------|--|
| pelvic abscess | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| peritonitis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 2 / 752 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pneumonia | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 5 / 382 (1.31%) | 15 / 752 (1.99%) | |
| occurrences causally related to treatment / all | 3 / 5 | 8 / 16 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| pneumonia chlamydial | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| postoperative wound infection | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| rectal abscess | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| respiratory tract infection | | | |
| alternative dictionary used: MedDRA 18.0 | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| retroperitoneal abscess | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| sepsis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 7 / 752 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 2 | |
| sinusitis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| skin infection | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| staphylococcal sepsis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| streptococcal infection | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|-----------------|-----------------|--|
| tonsillitis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 2 / 752 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| tooth abscess | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| upper respiratory tract infection | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 4 / 752 (0.53%) | |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| urinary tract infection | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 3 / 382 (0.79%) | 6 / 752 (0.80%) | |
| occurrences causally related to treatment / all | 3 / 3 | 3 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| vascular device infection | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 4 / 752 (0.53%) | |
| occurrences causally related to treatment / all | 1 / 1 | 6 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| viral upper respiratory tract infection | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| wound infection | | | |
| alternative dictionary used: MedDRA 18.0 | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| dehydration | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 7 / 752 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 6 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| diabetes mellitus inadequate control | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| fluid overload | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 0 / 752 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| fluid retention | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hypercalcaemia | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 1 / 382 (0.26%) | 4 / 752 (0.53%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hypocalcaemia | | | |
| alternative dictionary used: MedDRA 18.0 | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hypoglycaemia | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 2 / 752 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hypokalaemia | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 3 / 752 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hyponatraemia | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| lactic acidosis | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 0 / 382 (0.00%) | 1 / 752 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Placebo + Docetaxel | Ramucirumab (IMC-1121B) + Docetaxel | |
|---|---------------------|-------------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 373 / 382 (97.64%) | 737 / 752 (98.01%) | |
| Vascular disorders | | | |
| hypertension | | | |
| alternative dictionary used: MedDRA 18.0 | | | |

| | | | |
|---|--------------------|--------------------|--|
| subjects affected / exposed | 44 / 382 (11.52%) | 204 / 752 (27.13%) | |
| occurrences (all) | 96 | 405 | |
| hot flush | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 21 / 382 (5.50%) | 34 / 752 (4.52%) | |
| occurrences (all) | 22 | 44 | |
| General disorders and administration site conditions | | | |
| asthenia | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 127 / 382 (33.25%) | 270 / 752 (35.90%) | |
| occurrences (all) | 363 | 549 | |
| face oedema | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 27 / 382 (7.07%) | 73 / 752 (9.71%) | |
| occurrences (all) | 30 | 100 | |
| fatigue | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 135 / 382 (35.34%) | 271 / 752 (36.04%) | |
| occurrences (all) | 240 | 481 | |
| influenza like illness | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 29 / 382 (7.59%) | 39 / 752 (5.19%) | |
| occurrences (all) | 40 | 48 | |
| non-cardiac chest pain | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 19 / 382 (4.97%) | 39 / 752 (5.19%) | |
| occurrences (all) | 21 | 43 | |
| oedema | | | |
| alternative dictionary used: MedDRA 18.0 | | | |
| subjects affected / exposed | 18 / 382 (4.71%) | 43 / 752 (5.72%) | |
| occurrences (all) | 26 | 48 | |
| oedema peripheral | | | |
| alternative dictionary used: MedDRA 18.0 | | | |

| | | | |
|---|---|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>pyrexia</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>101 / 382 (26.44%)</p> <p>140</p> <p>44 / 382 (11.52%)</p> <p>65</p> | <p>181 / 752 (24.07%)</p> <p>274</p> <p>110 / 752 (14.63%)</p> <p>168</p> | |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>cough</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>dyspnoea</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>epistaxis</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>oropharyngeal pain</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>pleural effusion</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>rhinorrhoea</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>69 / 382 (18.06%)</p> <p>89</p> <p>75 / 382 (19.63%)</p> <p>90</p> <p>64 / 382 (16.75%)</p> <p>149</p> <p>27 / 382 (7.07%)</p> <p>36</p> <p>28 / 382 (7.33%)</p> <p>29</p> <p>19 / 382 (4.97%)</p> <p>23</p> | <p>127 / 752 (16.89%)</p> <p>179</p> <p>163 / 752 (21.68%)</p> <p>225</p> <p>300 / 752 (39.89%)</p> <p>817</p> <p>65 / 752 (8.64%)</p> <p>96</p> <p>69 / 752 (9.18%)</p> <p>74</p> <p>56 / 752 (7.45%)</p> <p>82</p> | |
| <p>Psychiatric disorders</p> <p>anxiety</p> <p>alternative dictionary used: MedDRA 18.0</p> | | | |

| | | | |
|--|--|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>27 / 382 (7.07%)</p> <p>27</p> <p>49 / 752 (6.52%)</p> <p>65</p> | | | |
| <p>insomnia</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>33 / 382 (8.64%)</p> <p>39</p> <p>99 / 752 (13.16%)</p> <p>127</p> | | | |
| <p>Investigations</p> <p>weight increased</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>92 / 382 (24.08%)</p> <p>105</p> <p>123 / 752 (16.36%)</p> <p>152</p> <p>weight decreased</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>41 / 382 (10.73%)</p> <p>50</p> <p>173 / 752 (23.01%)</p> <p>209</p> | | | |
| <p>Injury, poisoning and procedural complications</p> <p>infusion related reaction</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>24 / 382 (6.28%)</p> <p>43</p> <p>41 / 752 (5.45%)</p> <p>56</p> | | | |
| <p>Cardiac disorders</p> <p>tachycardia</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>23 / 382 (6.02%)</p> <p>36</p> <p>50 / 752 (6.65%)</p> <p>70</p> | | | |
| <p>Nervous system disorders</p> <p>dizziness</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>36 / 382 (9.42%)</p> <p>45</p> <p>64 / 752 (8.51%)</p> <p>88</p> <p>dysgeusia</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>32 / 382 (8.38%)</p> <p>66</p> <p>68 / 752 (9.04%)</p> <p>120</p> <p>headache</p> | | | |

| | | | |
|--|------------------------------------|--------------------------------------|--|
| <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>70 / 382 (18.32%)</p> <p>98</p> | <p>171 / 752 (22.74%)</p> <p>306</p> | |
| <p>neuropathy peripheral</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>64 / 382 (16.75%)</p> <p>78</p> | <p>101 / 752 (13.43%)</p> <p>124</p> | |
| <p>paraesthesia</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>31 / 382 (8.12%)</p> <p>40</p> | <p>47 / 752 (6.25%)</p> <p>59</p> | |
| <p>peripheral sensory neuropathy</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>73 / 382 (19.11%)</p> <p>90</p> | <p>136 / 752 (18.09%)</p> <p>193</p> | |
| <p>taste disorder</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>58 / 382 (15.18%)</p> <p>89</p> | <p>105 / 752 (13.96%)</p> <p>156</p> | |
| <p>Blood and lymphatic system disorders</p> <p>anaemia</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>28 / 382 (7.33%)</p> <p>39</p> | <p>77 / 752 (10.24%)</p> <p>108</p> | |
| <p>neutropenia</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>41 / 382 (10.73%)</p> <p>56</p> | <p>96 / 752 (12.77%)</p> <p>175</p> | |
| <p>Eye disorders</p> <p>lacrimation increased</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>65 / 382 (17.02%)</p> <p>90</p> | <p>233 / 752 (30.98%)</p> <p>337</p> | |
| Gastrointestinal disorders | | | |

| | | |
|---|--------------------|--------------------|
| abdominal pain | | |
| alternative dictionary used: MedDRA 18.0 | | |
| subjects affected / exposed | 42 / 382 (10.99%) | 95 / 752 (12.63%) |
| occurrences (all) | 59 | 141 |
| abdominal pain upper | | |
| alternative dictionary used: MedDRA 18.0 | | |
| subjects affected / exposed | 24 / 382 (6.28%) | 51 / 752 (6.78%) |
| occurrences (all) | 33 | 71 |
| constipation | | |
| alternative dictionary used: MedDRA 18.0 | | |
| subjects affected / exposed | 74 / 382 (19.37%) | 157 / 752 (20.88%) |
| occurrences (all) | 116 | 293 |
| diarrhoea | | |
| alternative dictionary used: MedDRA 18.0 | | |
| subjects affected / exposed | 152 / 382 (39.79%) | 326 / 752 (43.35%) |
| occurrences (all) | 338 | 751 |
| dry mouth | | |
| alternative dictionary used: MedDRA 18.0 | | |
| subjects affected / exposed | 20 / 382 (5.24%) | 29 / 752 (3.86%) |
| occurrences (all) | 33 | 54 |
| dyspepsia | | |
| alternative dictionary used: MedDRA 18.0 | | |
| subjects affected / exposed | 40 / 382 (10.47%) | 75 / 752 (9.97%) |
| occurrences (all) | 57 | 110 |
| gingival bleeding | | |
| alternative dictionary used: MedDRA 18.0 | | |
| subjects affected / exposed | 2 / 382 (0.52%) | 73 / 752 (9.71%) |
| occurrences (all) | 2 | 144 |
| haemorrhoids | | |
| alternative dictionary used: MedDRA 18.0 | | |
| subjects affected / exposed | 8 / 382 (2.09%) | 39 / 752 (5.19%) |
| occurrences (all) | 8 | 50 |
| nausea | | |
| alternative dictionary used: MedDRA 18.0 | | |

| | | | |
|---|--------------------------------------|--------------------------------------|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>156 / 382 (40.84%)</p> <p>343</p> | <p>278 / 752 (36.97%)</p> <p>766</p> | |
| <p>stomatitis</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>118 / 382 (30.89%)</p> <p>215</p> | <p>380 / 752 (50.53%)</p> <p>833</p> | |
| <p>vomiting</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>80 / 382 (20.94%)</p> <p>127</p> | <p>155 / 752 (20.61%)</p> <p>288</p> | |
| <p>Skin and subcutaneous tissue disorders</p> <p>alopecia</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>279 / 382 (73.04%)</p> <p>287</p> | <p>535 / 752 (71.14%)</p> <p>550</p> | |
| <p>dry skin</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>21 / 382 (5.50%)</p> <p>21</p> | <p>55 / 752 (7.31%)</p> <p>60</p> | |
| <p>nail disorder</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>105 / 382 (27.49%)</p> <p>114</p> | <p>231 / 752 (30.72%)</p> <p>250</p> | |
| <p>palmar-plantar erythrodysesthesia syndrome</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>33 / 382 (8.64%)</p> <p>36</p> | <p>106 / 752 (14.10%)</p> <p>157</p> | |
| <p>pruritus</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>21 / 382 (5.50%)</p> <p>23</p> | <p>41 / 752 (5.45%)</p> <p>44</p> | |
| <p>rash</p> <p>alternative dictionary used: MedDRA 18.0</p> | | | |

| | | | |
|--|--------------------------|---------------------------|--|
| subjects affected / exposed occurrences (all) | 47 / 382 (12.30%) 63 | 109 / 752 (14.49%) 143 | |
| Renal and urinary disorders proteinuria alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all) | 5 / 382 (1.31%) 5 | 44 / 752 (5.85%) 75 | |
| Musculoskeletal and connective tissue disorders arthralgia alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all) | 82 / 382 (21.47%) 167 | 173 / 752 (23.01%) 359 | |
| back pain alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all) | 54 / 382 (14.14%) 74 | 114 / 752 (15.16%) 143 | |
| bone pain alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all) | 41 / 382 (10.73%) 82 | 92 / 752 (12.23%) 192 | |
| musculoskeletal pain alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all) | 18 / 382 (4.71%) 32 | 51 / 752 (6.78%) 105 | |
| myalgia alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all) | 89 / 382 (23.30%) 209 | 153 / 752 (20.35%) 292 | |
| pain in extremity alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all) | 47 / 382 (12.30%) 66 | 107 / 752 (14.23%) 195 | |
| Infections and infestations | | | |

| | | | |
|---|--------------------------|---------------------------|--|
| conjunctivitis alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all) | 17 / 382 (4.45%) 25 | 38 / 752 (5.05%) 42 | |
| nasopharyngitis alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all) | 20 / 382 (5.24%) 30 | 63 / 752 (8.38%) 79 | |
| upper respiratory tract infection alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all) | 21 / 382 (5.50%) 29 | 39 / 752 (5.19%) 48 | |
| urinary tract infection alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all) | 28 / 382 (7.33%) 32 | 71 / 752 (9.44%) 91 | |
| Metabolism and nutrition disorders decreased appetite alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all) | 62 / 382 (16.23%) 101 | 165 / 752 (21.94%) 293 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 18 July 2008 | Important overall changes included additional instructions related infusion and shelf life of Ramucirumab, and instructions to report any Grade 3 or 4 AE as an 'important medical event' using the serious adverse event report (SAER) form. |
| 23 April 2009 | Important overall changes included new details on prohibited therapies, expanded to include hormonal therapy; additional instructions related to the preparation and administration of study drugs, and SAEs reporting. |
| 06 December 2010 | Important overall changes included the addition of an inclusion criterion to specify that participants that received prior biologic therapy in the metastatic setting were not eligible, changes to the interim analyses plan, with a reduction to one single analysis at 40% of the expected PFS events; updates to the unblinding procedures and reporting SAEs and other updates in different sections of the protocol, including pre-medications. |
| 23 April 2012 | Important overall changes included updates on the assessment of PFS and response-related endpoints, clarifications and details related to the OS analysis, additional instructions for the management of the reversible posterior leukoencephalopathy syndrome (RPLS) and other more administrative updates. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

One participant assigned to placebo + docetaxel (doc) treatment and was given ramucirumab (ram) in Cycle 1. Considered ram + doc treatment arm for safety population, for ITT population the participant was analyzed according to assigned treatment.

Notes: